CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://zenodo.org/records/13743063

https://www.iajps.com/volumes/volume11-march-2024/34-issue-03-march-24/

Available online at: http://www.iajps.com Research Article

FORMULATION AND EVALUATION OF SUBLINGUAL TABLETS OF POORLY AQUEOUS-SOLUBLE DRUG TICAGRELOR USING SUPERDISINTEGRANTS

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Article Received: January 2024 Accepted: February 2024 Published: March 2024

Abstract:

Ticagrelor is an oral antiplatelet drug that is used to decrease the risk of myocardial infarction and stroke in patients with acute coronary syndromes. Sublingual tablets, which disintegrate in the oral cavity beneath the tongue in less than a minute, are solid dosage forms that have the benefit of avoiding first-pass metabolism. The need for sublingual has increased over the past ten years, particularly among the elderly and kids who have swallowing issues. To achieve rapid disintegration in gastric pH and quick action as an oral antiplatelet agent, the current study's goal was to create sublingual tablets of Ticagrelor using various concentrations of Crosscarmellose Sodium, Sodium starch glycolate, and Cross povidone as superdisintegrants. There are twelve different sublingual tablet formulations were created using wet granulation technology. There is no interaction between the medications and the numerous excipients employed in the formulation, according to FTIR technology studies on the compatibility of drugs and excipients. When compared to the pharmacopeia, the outcomes of the various precompression and postcompression characterizations of tablets were satisfactory. Using a USP II paddle-type dissolution equipment, in vitro release experiments for several formulations were carried out. Formulation TSF_{12}, which contains 2% Crosscarmellose Sodium and 2% Cross povidone, demonstrated complete drug release in less than 30 minutes (>99%), establishing itself as an optimized formulation. Using both superdisintegrants in tandem also demonstrated an improved drug release profile. The zero-order kinetic model was the best formulation. Accelerated stability studies for improved formulation were done to confirm the stability of dosage forms.

Keywords: *Ticagrelor, Sublingual tablet, Croscarmellose Sodium, Sodium starch glycolate, Cross povidone, antiplatelet drug.*

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Please cite this article in press Niranjan Panda et al, ***Formulation And Evaluation Of Sublingual Tablets Of Poorly Aqueous-Soluble Drug Ticagrelor Using Superdisintegrants.,****Indo Am. J. P. Sci, 2024; 11 (3).*

INTRODUCTION:

The oral route is one of the most frequently utilized drug administration techniques. Tablets continue to be the most popular dosage form due to their constant innovation and adoption of fresh concepts to overcome the fundamental shortcomings of the current formulations. Placing the medication under the tongue is known as sublingual administration. The medicine is absorbed 3–10 times more quickly through the sublingual method than it is through the oral route. [1] Different formulations, including pills, films, and sprays, help administer medications sublingually. [2,3] The creation of sublingual dosage forms is a very difficult process. Mechanical strength, disintegration speed, flavor masking, tongue feel, susceptibility to environmental conditions, cost, and other factors are problems. Superdisintegrant is a key component in the production of sublingual tablets, together with other often used excipients including diluents, binders, lubricants, glidants, etc. The sublingual tablets are commonly produced using a range of superdisintegrants, such as sodium starch glycolate (Primojel), croscarmellose (AC-Di-Sol), and various grades of crosspovidone (Polyplasdone-XL), for quick and easy tablet disintegration. Wet granulation has gradually increased tablet production over time because of its consistent content and favorable compressibility profile. [4,5]

Ticagrelor is an oral antiplatelet drug that is used to decrease the risk of myocardial infarction and stroke in patients with acute coronary syndromes. Ticagrelor has been linked to rare instances of hypersensitivity reactions accompanied by mild liver injury. Ticagrelor is an orally administered direct-acting $P2Y_{12}$-receptor antagonist. *In vitro* studies have demonstrated that ticagrelor binds reversibly and noncompetitively to the $P2Y_{12}$ receptor at a site distinct from that of the endogenous agonist adenosine diphosphate (ADP). Ticagrelor was rapidly absorbed after oral administration (median t_{max} = 1.49 h) and the median t_{max} for ticagrelor following IV administration (0.48 h) coincided with the end of the infusion. The steady state volume of distribution of ticagrelor is 88 L. After absorption, ticagrelor and AR-C124910XX are highly bound to plasma proteins (more than 99.8%) and largely restricted to the plasma. Ticagrelor is metabolized and transformed into AR-C124910XX predominantly by CYP3A4 and CYP3A5 enzymes. The primary route of ticagrelor elimination is hepatic metabolism. The primary route of elimination for the major metabolite of ticagrelor is most likely to be biliary secretion. The mean $t_{½}$ is approximately 7 hours for ticagrelor and 9 hours for the active metabolite. Therefore, the metabolism of ticagrelor is affected by the concomitant administration of strong CYP3A inducers or inhibitors. The renal clearance of ticagrelor is 0.00584L/h. In patients with chronic kidney disease (creatinine clearance <60 mL/min; n=3237). [6] Ticagrelor is soluble in organic solvents such as ethanol, DMSO, and dimethyl formamide (DMF). The solubility of ticagrelor in these solvents is approximately 15, 20, and 25 mg/ml, respectively. Ticagrelor is sparingly soluble in aqueous buffers. Ticagrelor belongs to the BCS class II drug. It is recommended that adults take 60 mg twice daily. [7]

The primary objective of the recent studies was to design and carry out *in vitro* evaluation tests of sublingual Ticagrelor tablets using super disintegrants like sodium starch glycolate, crosscarmellose and crosspovidone to achieve rapid dispersion when taken through the buccal cavity, bypassing first-pass metabolism and allowing a rapid onset of action. [8]

MATERIALS AND METHODS:

Materials

Ticagrelor was acquired from Dr. Reddy's laboratories Pvt. Ltd. Hyderabad, as gift sample. Also provided from Dr. Reddy's Laboratories Pvt. Ltd. was a gift sample of the superdisintegrant sodium starch glycolate, crosscarmellose and crosspovidone. The diluent was purchased from Otto Manufacturers. MCC, mannitol, PVP K30, talc, and magnesium stearate were purchased from S.D. Fine Chemicals Pvt. Ltd. in Mumbai, India. Each component was of the highest caliber for a lab. The double distillation method was used in the lab to produce the distilled water that was used in the study.

METHODS

Analytical method for the *in vitro* estimation of Ticagrelor in the formulations

A primary stock solution of Ticagrelor with a concentration of 1000 g/ml was made using a phosphate buffer with a pH of 6.8. Following the proper dilution, a secondary stock solution with a concentration of 10 µg/ml was made from the initial stock solution using the same phosphate buffer pH 6.8. The created secondary stock solution's greatest absorbance was found to be 222 nm, which was picked and used for further investigation after being scanned with a UV spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at wavelengths ranging from 400 nm to 200 nm. Using the same phosphate buffer pH 6.8, the secondary stock solution was first diluted to produce a series of concentrations of 2, 4, 6, 8, and 10 µg/ml. Then, the absorbance at the maximum wavelength of 222 nm was determined. Plotting observed absorbencies against matching

concentrations resulted in the calibration curve of pure Ticagrelor. [9, 10]

Drug and excipient compatibility studies

Drugs and excipients used for the formulation of different batches of Ticagrelor sublingual tablets were analyzed for any possible physical and chemical interactions through FTIR.

Fourier Transform Infrared (FTIR) spectroscopy

Fourier transforms infrared (FTIR) spectroscopy tests were performed to identify the peaks in the pure medicine and the excipients used that indicate the existence of a specific functional group. If the functional groups present in the pure drug are replicated in the formulations, the drug and excipients are deemed to be compatible. Both the pure drug and a physical mixture of the drug and all excipients were investigated using FTIR with Ticagrelor (optimized formulation). The pellet technique and potassium bromide were employed in the operation (KBr). After the components had been triturated with KBr, a pellet was made by exerting pressure of 100 kg/cm^2 for two minutes. The obtained pellet was investigated in the FTIR 8400S by Shimadzu, Japan. The analysis of the test samples came first, followed by the acquisition of the KBr backdrop. The same steps were performed for the analysis of the drug, each excipient, and the physical mixing of the excipients and the drug. [11, 12]

Differential scanning calorimeter (DSC) investigation:

A Shimadzu DSC-60 (Shimadzu, Kyoto, Japan) apparatus was used for the DSC study. Both a pure drug Ticagrelor and a mixture (Ticagrelor plus excipients), had their DSC thermograms collected. DSC aluminum cells served as the sample container and the reference, respectively. A sample of 2-3 mg was used for analysis. Under nitrogen purge at a rate of 20 ml/min, thermograms were taken over the temperature range of 20°C-200°C at a constant rate of 20°C/min. Figures 3 and 4 show the results. [13]

Formulation of Ticagrelor Sublingual tablets (TSF$_1$- TSF$_{12}$)

Ticagrelor sublingual tablets were created using the wet granulation process. Before being used in formulations, all materials were weighed precisely and put through filter #80. Ticagrelor, MCC, mannitol, sodium starch glycolate, croscarmellose, crosspovidone, and saccharine were just a few of the powders that were combined equally and passed through #20 for each composition. The binder utilized was PVP K30. To lower the moisture content and prevent sticking to the sieve, the aggregates created after the addition of the binder were first dried for five to ten minutes. To obtain granules, the aggregates were sent through filter #20. To lower the moisture content of the granules by up to 2-5%, they are dried at 40° C for 20 minutes. Talc and magnesium stearate were utilized as lubricants, and dried granules were combined with the necessary amounts for 2–3 minutes. Before compression, the formulations' angle of repose, bulk density, tapped density, compressibility index, and Hausner's ratio were assessed after lubrication. On a 10-station rotary punching machine (Saimach Pharmaceutical Pvt. Ltd.), using 8 mm concave punches, the evaluated granules were compressed into tablets. Ticagrelor, 60 mg, is present in each tablet. Table 1 contains the recipes for many formulations, and the same process was used for each formulation. Then, different post-compression parameters were assessed for the generated sublingual tablet formulations, including average thickness, weight variation, hardness, friability, drug content study, disintegration, and in vitro dissolving experiments. [14. 15]

Table 1: Compositions of different formulations of Ticagrelor Sublingual tablets

Formulations(mg)	TSF$_1$	TSF$_2$	TSF$_3$	TSF$_4$	TSF$_5$	TSF$_6$	TSF$_7$	TSF$_8$	TSF$_9$	TSF$_{10}$	TSF$_{11}$	TSF$_{12}$
Ticagrelor	60	60	60	60	60	60	60	60	60	60	60	60
MCC	88	86	84	88	86	84	88	86	84	86	86	86
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
Crosscarmellose Sodium	6	8	10	---	---	---	---	---	---	4	---	4
SSG	---	---	---	6	8	10	---	---	---	4	4	---
Cross povidone	---	---	---	---	---	---	6	8	10	---	**4**	**4**
PVP K30	20	20	20	20	20	20	20	20	20	20	20	20
Saccharine	1	1	1	1	1	1	1	1	1	1	1	1
Mg. Stearate	3	3	3	3	3	3	3	3	3	3	3	3
Talc	2	2	2	2	2	2	2	2	2	2	2	2
Total wt.	200	200	200	200	200	200	200	200	200	200	200	200

Evaluation of precompression parameters of dry granules of Ticagrelor Sublingual tablet formulations

The angle of Repose (θ)

The dry granules were allowed to flow through the funnel fixed to a stand at a definite height (h). The angle of repose was then calculated by measuring the height and radius of the heap of granules formed.

$$\theta = \tan^{-1}\left(\frac{h}{r}\right)$$

Where θ was called the angle of repose, h and r were the height and radius of the granule heap respectively. According to the specifications, the angle of repose value less than 25^0 indicates excellent flow whereas an angle greater than 40^0 indicates poor flow. [16]

Bulk density and tapped density

Both the bulk density (BD) and tapped density (TD) of prepared dry granules of all the formulations were determined using the following formulas. [16]

$$BD = \frac{weight\ of\ the\ dry\ powder}{volume\ of\ the\ packing}$$

$$TD = \frac{weight\ of\ the\ dry\ powder}{tapped\ volume\ of\ the\ packing}$$

Compressibility Index (Carr's index):

The flow ability of powder can be evaluated by comparing the bulk density (BD) and tapped density (TD) of granules and the rate at which it is packed down. The compressibility index (Carr's index) of prepared dry granules was calculated by following the formula

$$Carr's\ index\ (\%) = \frac{TD-BD}{TD} \times 100$$

According to the specification, Carr's index values "between" 5-15 indicate excellent flow whereas between 12-16 indicates good flow. Values "between" 18-21 indicate fare-passable whereas between 23-25 indicates poor. "Between" 33-38 indicates very poor and greater than 40 indicates extremely poor. [16]

Hausner's ratio:

The Hausner's ratios of prepared Ticagrelor Sublingual dry granules were determined by following the formula.

$$Hausner's\ ratio = \frac{TD}{BD}$$

According to specifications values less than 1.25 indicate good flow (=20% of Carr's index), whereas greater than 1.25 indicates poor flow (=33% of Carr's index). Between 1.25 and 1.5, glidant needs to be added to improve flow. [17]

Evaluation of post-compression parameters of Ticagrelor Sublingual tablets (TSF) formulations

Typical thickness

Ten tablets were randomly chosen from each formulation (TSF) and utilized for thickness measurement. Using digital Vernier callipers (Mitutoyo dial Thickness Gauge, Mitutoyo, Japan), the thickness of each tablet was measured. The results were expressed as the mean values of 10 readings with standard deviations. Tablet thickness should be kept within 5% of the standard value, as per the specification. [18]

Tablet Hardness

Using a Monsanto hardness tester, the hardness of all Ticagrelor Sublingual tablet formulations was determined (Cad Mach). Ten Sublingual tablets with known weights from each formulation were tested for crushing strength, which was measured in kg/cm^2, averaged, and then shown with standard deviation. According to USP requirements, a sublingual tablet's hardness value of 3–4 kg is deemed sufficient for mechanical stability. [18]

Friability

Ten tablets (TSF) from each batch that had previously been weighed were placed in the Roche friabilator (Roche friabilator, Secor India). Tablets were found after a hundred friabilator revolutions. The tablets were then cleaned of dust, and the total weight that remained was noted. This formula was used to determine friability.

$$\%F = \frac{(Wi - Wf)}{Wi} \times 100$$

the starting and final weights of the tablets prior to and following the friability test, respectively, were Wi and Wf. Compressible tablets that lose between 0.1% and 0.5% and, at most, 1% of their weight are deemed acceptable. Weight fluctuation test [19]

Weight variation test

The weight variation of each formulation was assessed in accordance with the USP standard. Using an electronic balance, 20 pills from each batch were weighed both collectively and individually. Calculations were made on the average weight and % variance of each tablet. The USP standard states that the weight variation tolerance limit for uncoated tablets with an average weight of 130 mg or less is 10%, 7.5% for tablets with an average weight between 130 and 324 mg, and 5% for tablets with an average weight of more than 324 mg. The weight of the tablet must not differ from the average weight by

more than two tablets' weight, and no tablet may deviate by more than 15%. [19]

Content uniformity

Twenty pills were ingested and triturated into powder to test the content homogeneity of all formulations (TSF). One tablet's worth of powder was taken, diluted in 100 ml of phosphate buffer with a pH of 6.8, and heated at 37 ^{0}C for 15 to 20 minutes while stirring continuously. The Ticagrelor concentration was determined using a UV Spectrophotometer (Analytical Technologies Ltd. Spectro 2080) at 222 nm after the solution had been cooled, filtered, and appropriately diluted. The average medication content of each formulation was computed after each measurement was made in triplicate. [20]

Wetting time and water absorption ratio

The disintegrating process of the tablet formulation is reflected in the wetting time. The disintegration rate increases as wetting time decreases. Twice-folded tissue paper was placed in a petri dish with an internal diameter of 6.5 cm, 10 ml of phosphate buffer pH 6.8, and 0.1% w/v of methylene blue for the purpose of determining the wetting time. Ticagrelor sublingual tablet samples from each formulation were meticulously arranged on the tissue paper in the petri plate. Wetting time was measured as the length of time it took for the dye to reach the tablet's top surface. The standard deviations were also calculated, and measurements were done in triplicate. The weight (W_b) of the tablet before it is placed on the Petri dish, followed by the observation of the wetting period, can be used to determine the water absorption ratio (R). The wet tablet was taken out and weighed again (Wa). The following equation was used to calculate the water absorption ratio. [21]

$$R = \frac{(Wa - Wb)}{Wb} \times 100$$

***In vitro* disintegration time (D_t)**

The USP specifies 2 minutes as the acceptable time limit for tablet disintegration meeting official criteria, whereas 2 minutes for sublingual dosage form when using the disintegration apparatus for oral tablets without the covering plastic discs. The experiment was conducted using a tablet disintegration device (model EI D-16, Electrolab, Mumbai, India). A modified disintegration method was used to conduct an in vitro disintegration test on a disintegration tester that was kept at 37℃ ± 0.5℃ in phosphate buffer pH 6.8 (n = 6). The time it took for each pill to totally break down into smaller particles was observed while the tablets were stored in the basket. [22]

***In vitro* drug release (dissolution) study**

Utilizing an eight-station USP dissolution rate test apparatus Type-II, the *in vitro* dissolution investigation was carried out for all of the formulations (TSF) (LABINDIA DS 8000, Mumbai, India.). The dissolution medium, a total volume of 900 ml of phosphate buffer pH 6.8, was kept at 37℃ ± 0.5℃ at 50 rpm. At regular intervals, 5ml of aliquots were removed and replaced with an equivalent volume of a new dissolving medium. Samples were taken every 5 minutes and then filtered using Whatmann filter paper. Ticagrelor released from sublingual tablets was determined by spectrophotometric analysis of samples at 222 nm. [23]

Characterization of the *in vitro* drug release profile

The rate and mechanism of release of Ticagrelor from prepared sublingual tablets were analyzed by fitting the dissolution data into the following exponential equations.

Zero order release equation is calculated by the following equation.

$$Q = K_0 t$$

Where Q is the amount of drug released at time t and K_0 is the zero-order release rate constant.

The first-order equation is calculated by following the equation.

$$\log(100 - Q) = log100 - K_1 t$$

Where K_1 is the first order release rate constant. [25, 26]

Stability studies of the best formulation

The short-term stability studies of the best formulation were carried out according to ICH guidelines. The best formulation was subjected to accelerated stress condition at 40 ºC ± 2 ºC/ 75% ± 5% RH for 90 days. After that period the product was evaluated for friability, hardness, weight variation, thickness, drug content, and *in vitro* drug release study. [27, 28]

RESULTS AND DISCUSSION:

Drug-Excipient Compatibility studies by FTIR:

By comparing the spectra of the pure Ticagrelor drug and Ticagrelor with excipients used in formulation, it can be seen that the broad peak that appeared at 3440 cm^{-1} also appears in Ticagrelor with excipients used in formulation at 3425 cm^{-1} due to N-H stretching and the sharp peaks that appear in spectra of Ticagrelor at 2909 cm^{-1} appear at 2925 cm^{-1} due to -CH stretching. Due to CH stretching, the broad peak that was seen at 3290 cm^{-1} also emerges at 3291 cm^{-1} in the physical mixing of ticagrelor with formulation excipients (Alkene). O-H stretching causes the broad peak that emerged at 3640 cm^{-1} to likewise appear at 3620 cm^{-1}

in the physical mixing of ticagrelor with formulation excipients (Free). The physical mixture of ticagrelor with the excipients used for formulation contained the characteristic IR absorption peaks of ticagrelor at 1584 cm-1 (C=C stretching (Aromatic)), 1509 cm-1 (N-H bending), 1327 cm^{-1} (CH bending (alkane)), 1039 cm^{-1} (C-N vibration), 1097 cm^{-1} (O-H bending (Alcohol)), and 888 cm^{-1} (CH bending (aromatic). Therefore, it is clear from the fact that all of the characteristic peaks that were present in the spectra of pure drugs were almost exactly replicated in the same region in the spectra of the best formulations of Ticagrelor sublingual tablet that there is no meaningful interaction between the drugs and the excipients. **Figures 1 and 2** display the FTIR spectra of the medication Ticagrelor in its purest form and the finest formulations.

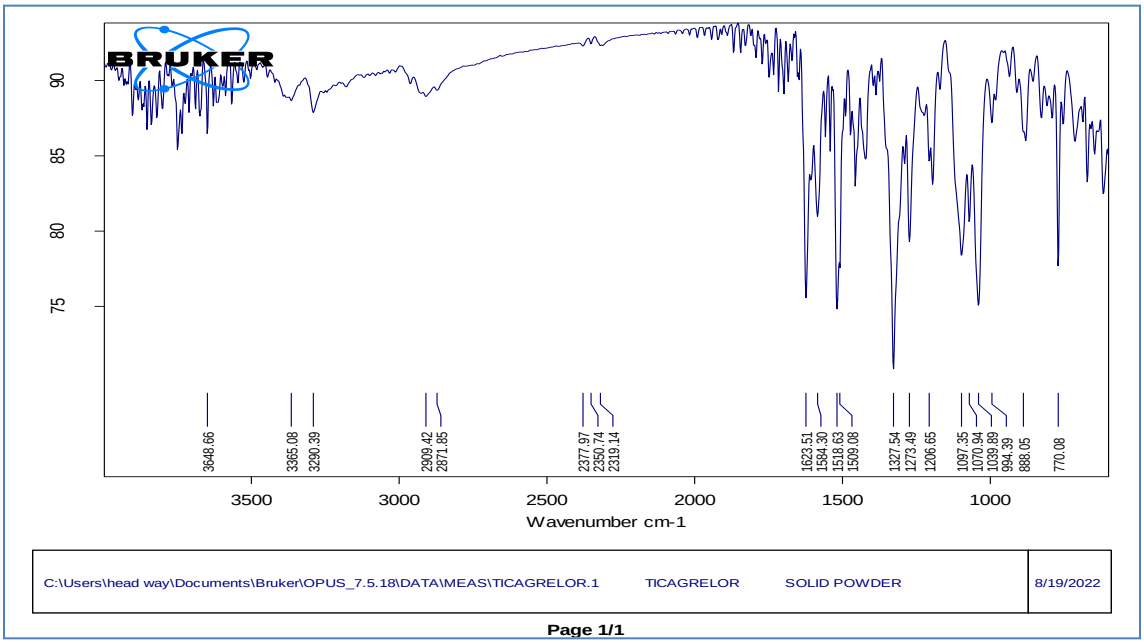

Fig. 1: FT-IR spectra of Ticagrelor pure drug

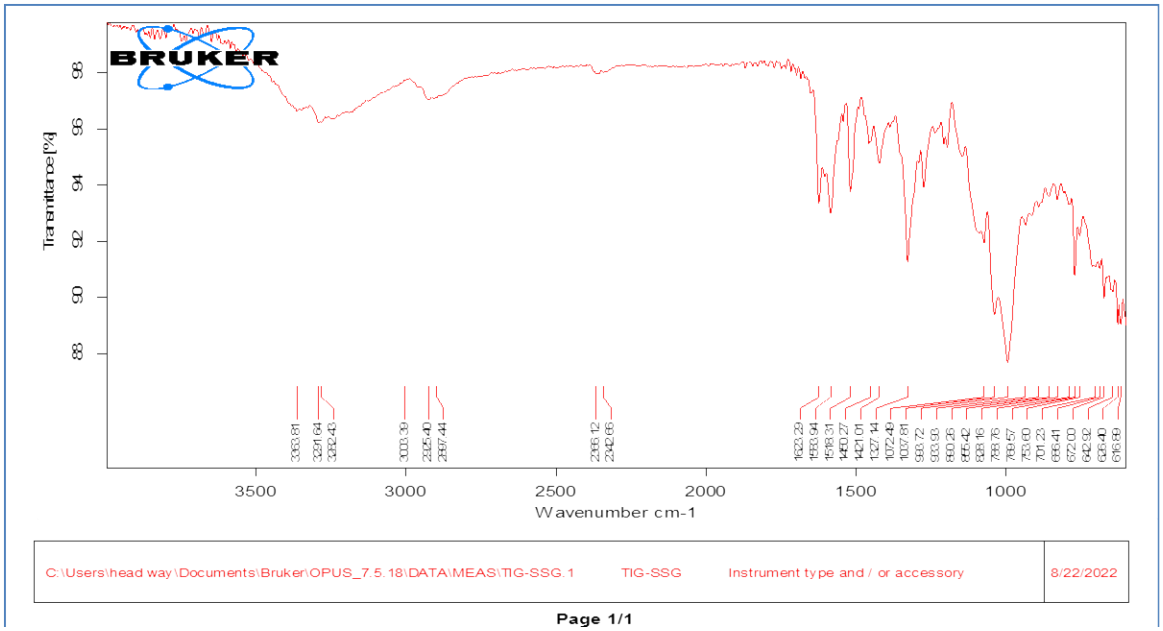

Fig. 2: FT-IR spectra of physical mixture of Ticagrelor with excipients

DSC Studies:

To rule out any potential drug and polymer thermal interaction, ticagrelor's DSC thermogram and a physical mixture of ticagrelor and the excipients utilized in the formulation of sublingual tablets were obtained. The endothermic peaks that formed in the pure drug and the physical mixture of the drug and excipients utilized to create the sublingual tablet were compared in this investigation. It was noted that the endothermic peak for ticagrelor emerged at 142.5℃ and in the physical mixture at 142.37℃. In the DSC thermogram of the physical mixture, endothermic peaks were present at 150.2ºC and 205.25ºC, respectively, because of the excipients crospovidone, croscarmellose sodium, and sodium starch glycolate. According to the aforementioned DSC investigations, the formulation is thermodynamically stable because it required approximately the same amount of heat as the pure medication and the inclusion of various excipients in the drug didn't result in any thermal changes. Additionally, no endothermic to exothermic peak shifting was observed. Figures 3 and 4 display the DSC thermograms for ticagrelor and the physical mixture of ticagrelor and excipients utilized in the manufacture of sublingual tablets.

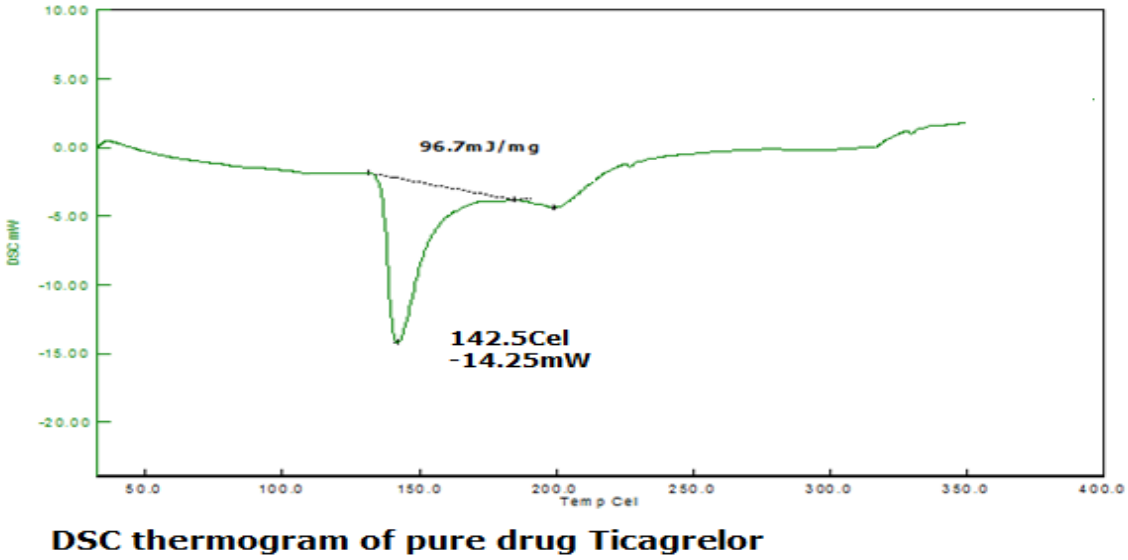

Fig. 3: DSC thermogram of Ticagrelor pure drug

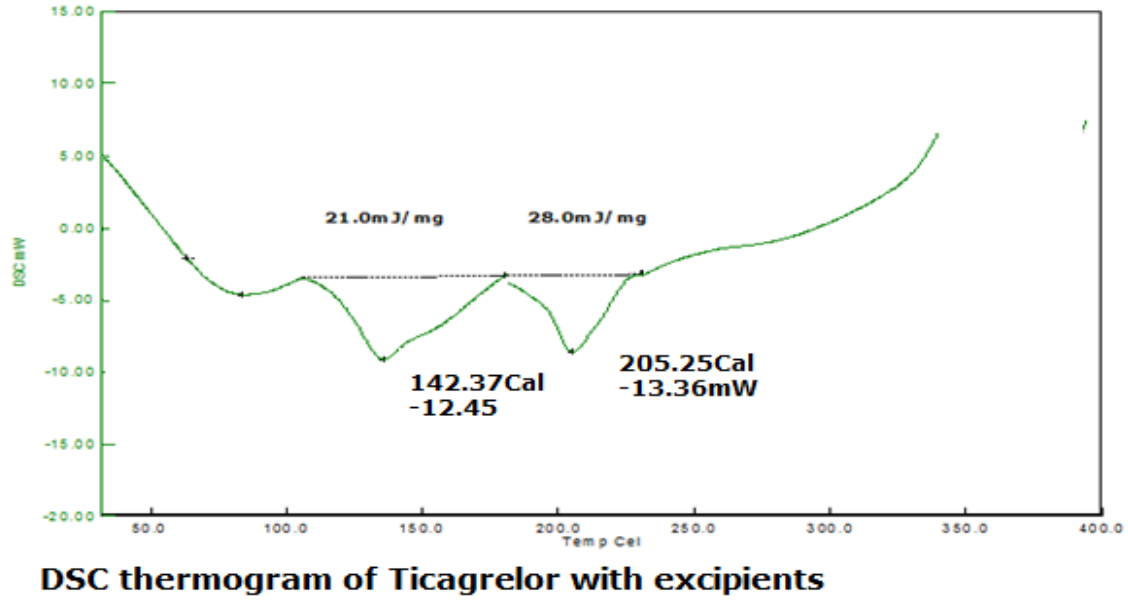

Fig. 4: DSC Thermogram of optimized Ticagrelor Sublingual tablets

Precompression parameters

The bulk densities of all formulations of Ticagrelor sublingual dry granules were determined to be between 0.415±0.002 to 0.455±0.003 g/cm3, and the tapped densities were found to be between 0.470±0.002 and 0.498±0.001 g/cm3. This suggests that dry granules have considerable packing capacity. According to measurements of bulk density and tapped density, the density of dry granules depends on particle packing and alters when the granule consolidates. The values of Carr's index for all of the formulations were found to be below 16%, which typically indicates favorable flow characteristics. The Hausner's ratio is an easy way to gauge flow characteristics and assess the stability of the power and granule column. The Hausner's ratio showed a low range, which denotes good flow capacity. The Hausner's ratios varied from 1.08 to 1.16 in all formulations, indicating good flow properties for dry granules. The angle of repose is appropriate for particles larger than 150 m. Angles of repose values between 25 and 30 often imply poorly flowing materials and free-flowing materials, respectively. The flowability of the dry powder or grains is indicated by the angle of repose. All formulations had angles of repose that ranged from 20.78±0.45 to 22.46±0.39, meaning that the dry granules of the Ticagrelor sublingual tablet exhibited good flow characteristics and were suitable for compression. Table 2 lists the precompression parameter results for each formulation.

Table 2: Evaluation of precompression parameters of Ticagrelor sublingual dry granules (TSF_1 – TSF_{12})

F. No.	Bulk density (gm/ml)	Tapped density (gm/ml)	Angle of repose (θ)	Carr's index (%)	Hausner's ratio	Drug Content (%)
TSF_1	0.415±0.002	0.473±0.002	20.78±0.45	12.26	1.14	97.36±0.34
TSF_2	0.428±0.003	0.465±0.001	21.62±0.41	09.03	1.08	101.86±0.65
TSF_3	0.430±0.002	0.478±0.002	21.45±0.66	10.04	1.11	99.65±0.39
TSF_4	0.436±0.002	0.492±0.003	21.25±0.30	11.38	1.23	99.36±0.53
TSF_5	0.421±0.002	0.473±0.001	22.35±0.19	10.99	1.12	98.62±0.88
TSF_6	0.442±0.003	0.495±0.003	21.36±0.24	10.70	1.12	99.35±0.36
TSF_7	0.443±0.002	0.489±0.003	21.61±0.35	09.41	1.10	98.63±0.60
TSF_8	0.436±0.003	0.481±0.002	21.36±0.24	09.35	1.10	99.34±0.66
TSF_9	0.455±0.003	0.498±0.001	22.46±0.39	08.63	1.09	99.67±0.52
TSF_{10}	0.428±0.001	0.472±0.002	21.41±0.24	09.32	1.10	98.34±0.67
TSF_{11}	0.425±0.001	0.470±0.002	19.34±0.24	09.57	1.11	101.32±0.54
TSF_{12}	0.412±0.002	0.478±0.001	20.65±0.36	13.80	1.16	99.38±0.25

All values are expressed as mean± SD; (n=3)

Post-compression parameters

The physical characteristics of all Ticagrelor Sublingual tablet formulations, including hardness, average weight variation, average friability, and average thickness, were found to be good. There were no signs of the typical tablet flaws that are capping, chipping, or picking. The tablets had average thicknesses that varied from 4.24±0.21 mm to 4.75±0.26 mm. Each batch had a uniform thickness and was within the acceptable limit. Percentage It was discovered that weight differences ranged from 2.33±0.34% to 3.87±0.12% for various formulations. All formulations passed the test for weight uniformity by the official criteria since the permissible average percentage variation for tablet formulations with a weight of 200 mg is 5%.

All of the prepared tablet formulations had an average hardness that ranged from 3.15±0.41 to 3.90±0.37 kg/cm2. The hardness is typically reduced with an increase in super-disintegrant content, as was the case with formulations TSF_3, TSF_6, and TSF_9. The percentage friability of all formulations ranged from 0.42±0.36% to 0.68±0.51%, and the concentration of the superdisintegrant was observed to increase the percentage friability. The percentage of friability in the current study was within the permitted ranges for all formulations. According to the formulations of Ticagrelor sublingual tablets, the percentages of drug content for TSF_1 to TSF_{12} ranged from 97.36±0.34% to 101.86±0.65%, which was within acceptable bounds. All formulations' disintegration times were measured, and it was discovered that the disintegration time lowers as superdisintegrant concentration rises above 6%, while the hardness value increases.

All of the formulas' wetting times ranged from 62±1.5 sec to 118±1.5 sec. About wetting time, wetting times for the formulations of TSF_3, TSF_6, TSF_9, TSF_{10}, TSF_{11}, and TSF_{12} decreased as super-disintegrant concentration was increased. When both the super disintegrants were used in combination, showed a shorter wetting time. The water absorption ratio increased with a rise in super-disintegrant concentration, which may have been caused by an increase in formulation porosity. **Table 3** lists the physicochemical descriptions of several batches of Ticagrelor Sublingual tablets.

Table 3: Evaluation of post-compression parameters of Ticagrelor Sublingual tablets

F. No.	Average hardness (kg/cm^2)	Average Weight Variation (%)	Average friability (% w/w)	Average thickness (mm)	Disintegration time (sec)	Wetting time (sec)
TSF_1	3.89±0.34	2.33±0.34	0.45±0.24	4.65±0.28	165±1.4	105±1.2
TSF_2	3.56±0.27	3.56±0.21	0.52±0.31	4.32±0.25	121±1.3	92±1.3
TSF_3	3.15±0.41	3.27±0.54	0.65±0.36	4.24±0.21	85±1.2	68±1.4
TSF_4	3.90±0.37	2.76±0.51	0.48±0.25	4.43±0.32	149±1.3	112±1.1
TSF_5	3.78±0.28	3.16±0.36	0.57±0.26	4.52±0.35	115±1.5	90±1.3
TSF_6	3.45±0.28	3.59±0.41	0.68±0.51	4.56±0.40	78±1.4	72±1.2
TSF_7	3.85±0.26	2.89±0.30	0.42±0.36	4.40±0.31	158±1.4	118±1.5
TSF_8	3.67±0.34	3.23±0.26	0.56±0.31	4.75±0.26	128±1.3	97±1.4
TSF_9	3.24±0.29	3.78±0.25	0.61±0.52	4.65±0.27	82±1.2	75±1.3
TSF_{10}	3.67±0.54	2.65±0.36	0.54±0.35	4.49±0.26	89±1.3	70±1.3
TSF_{11}	3.55±0.48	3.87±0.12	0.55±0.40	4.24±0.26	85±1.5	65±1.2
TSF_{12}	3.75±0.32	2.54±0.52	0.53±0.42	4.41±0.26	78±1.8	62±1.5

All values are expressed as average± SD; (n=3)

Sublingual Ticagrelor tablets from each batch (TSF_1 - TSF_{12} formulations) were tested for *in vitro* drug release using a USP XXIV type II dissolution device in phosphate buffer at a pH of 6.8. In figure 5, the cumulative drug release plotted as a function of time (min) is shown. Using a USP type-II paddle-type dissolution device, the *in vitro* drug release properties were investigated for a duration of 25 to 30 minutes in a phosphate buffer pH 6.8 dissolution medium. By increasing the concentration of superdisintegrant, the rate of dissolving increased, but above 4% as the hardness reduces, it was thought to be the ideal concentration. When both superdisintegrants are used together at a

total concentration of 4%, the dissolving profile is improved and the medicine is released virtually completely within 30 minutes. Formulation TSF_{12} releases the medication in 30 minutes and has a superdisintegrant concentration of 4% (2% cross povidone and 2% croscarmellose sodium). Mannitol and MCC performed well together as diluents, therefore it was employed in all of the formulations.

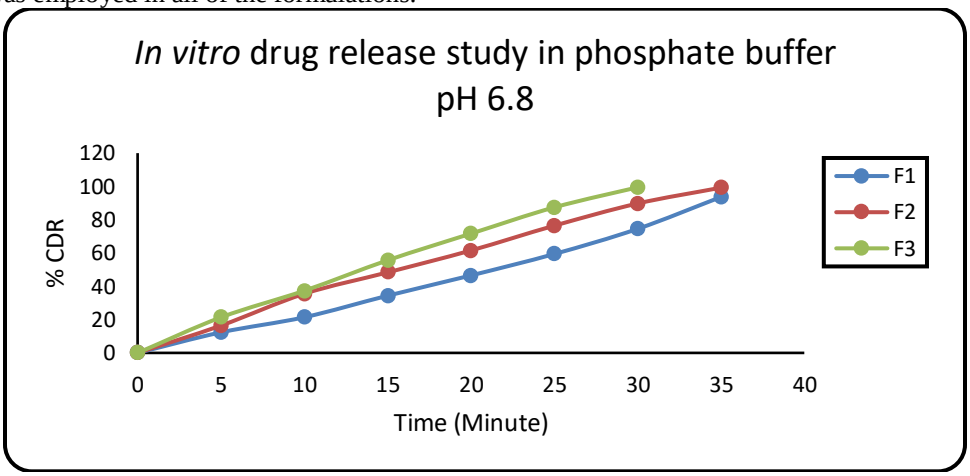

Fig. 5: *In vitro* drug release study of Ticagrelor Sublingual tablet formulations (TSF_1 to TSF_3)

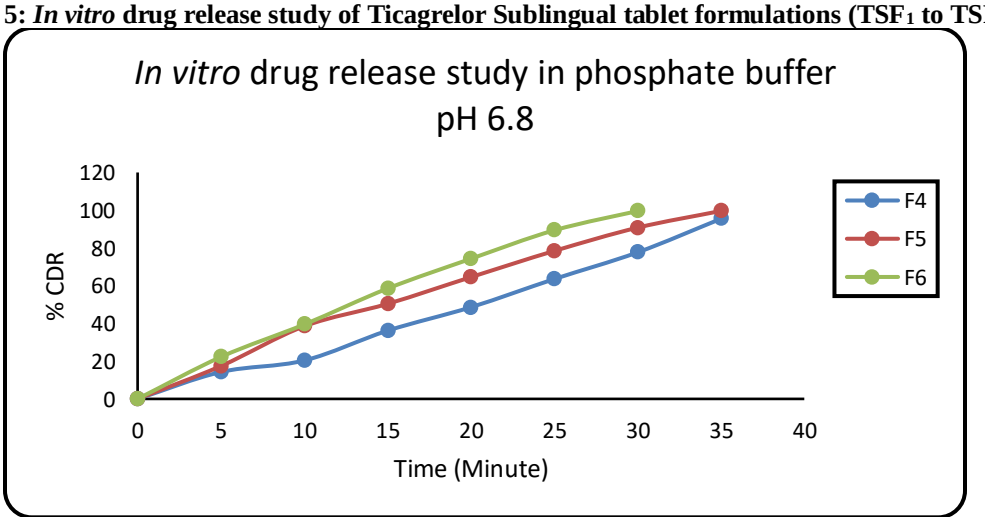

Fig. 6: *In vitro* drug release study of Ticagrelor Sublingual tablet formulations (TSF_4 to TSF_6)

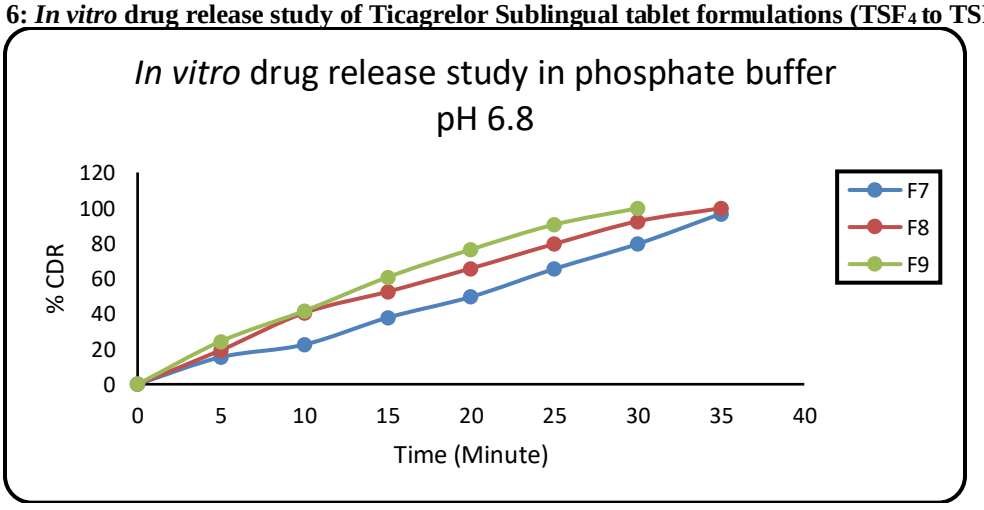

Fig. 7: *In vitro* drug release study of Ticagrelor Sublingual tablet formulations (TSF_7 to TSF_9)

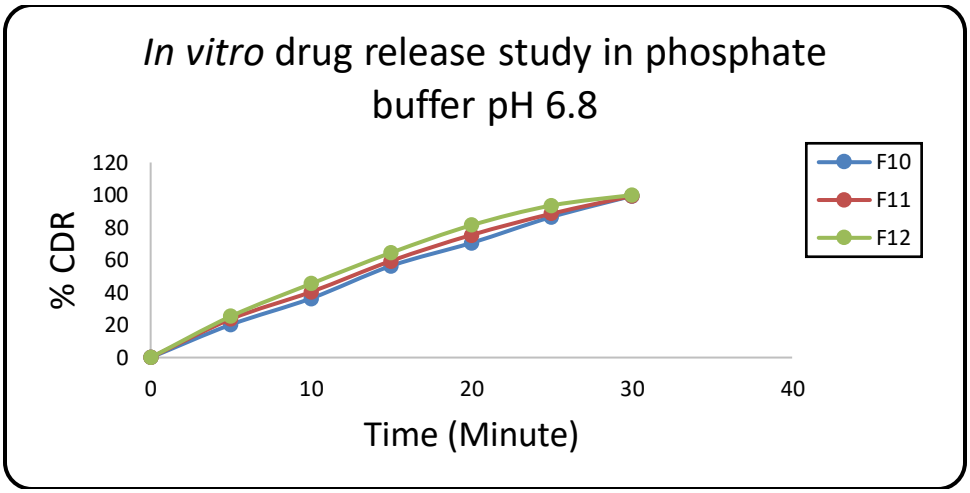

Fig. 8: *In vitro* drug release study of Ticagrelor Sublingual tablet formulations (TSF_9 to TSF_{12})

The optimized formulation of TSF_{12}'s *in vitro* dissolution study findings was put to the test for various kinetic release investigations, including zero-order and first-order kinetic models. The results' regression values were examined. Figure 9–10 displays the *in vitro* drug release kinetic analyses.

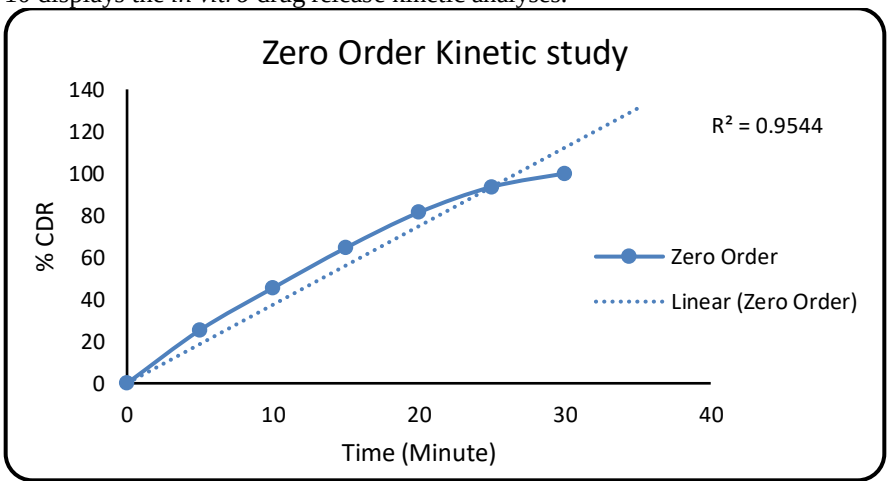

Fig. 9: Best formulation zero order kinetic studies (TSF_{12})

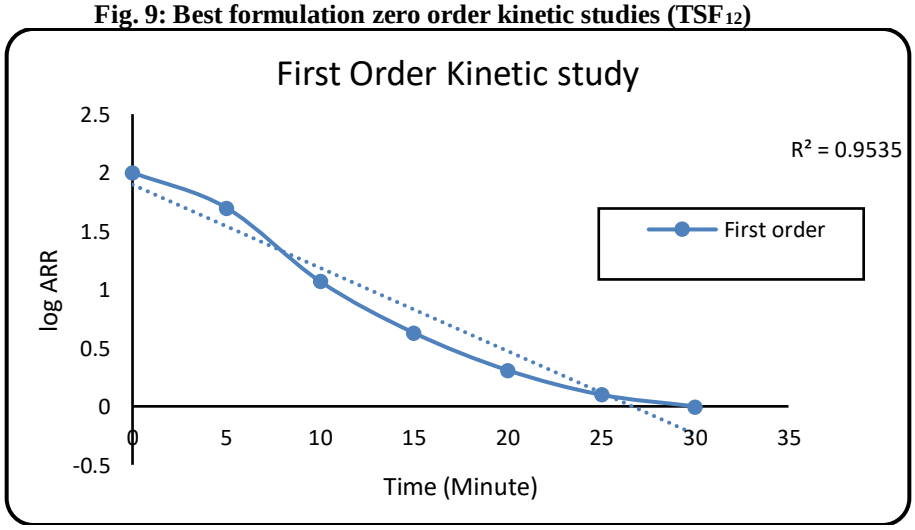

Fig. 10: Best formulation first order kinetic studies (TSF_{12})

The optimized formulation TSF_{12} underwent in vitro drug release kinetic investigations using a zero-order and first-order kinetic model. It was confirmed that the in vitro release kinetics adheres to the zero-order kinetic model based on the maximum regression value of R^2.

Table 4: Regression values of *in vitro* release kinetic study

Formulation	Regression coefficient of Zero-order	Regression coefficient of 1st order	Conclusion
Ticagrelor sublingual Tablet best formulations (TSF_{12})	0.9984	0.9535	Release kinetics follows zero order kinetic model

Different tablet physical characteristics, such as friability, hardness, weight fluctuation, thickness, and drug content, were compared. The optimized fresh formulation (TSF_{12}) was also tested *in vitro* before and after an accelerated stability study. The test satisfies the stability requirements.

Table 5: Comparative physicochemical properties of TSF_{12} at accelerated conditions (40 ° C ± 2 ° C/ 75% ± 5% RH)

Sl. No.	Physicochemical characteristics	Initial	After 30 days	After 60 days	After 90 days
1	Physical appearance	Pale white, circular, concave smooth surface without any cracks	No change	No change	No change
2	Weight variation	2.54±0.52	2.62±0.42	2.68±0.35	2.74±0.61
3	Hardness	3.75±0.32	3.80±0.40	3.92±0.51	3.98±0.45
4	Friability	0.53±0.42	0.56±0.21	0.60±0.32	0.64±0.41
5	Wetting time (Sec)	62±1.5	64±1.4	68±1.2	71±1.3
6	Drug content	99.38±0.25	97.61±0.33	95.37±0.52	94.10±0.23
7	D_t (Sec)	78±1.8	85±1.3	89±1.3	95±1.6

All values are expressed as mean± SD; (n=3)

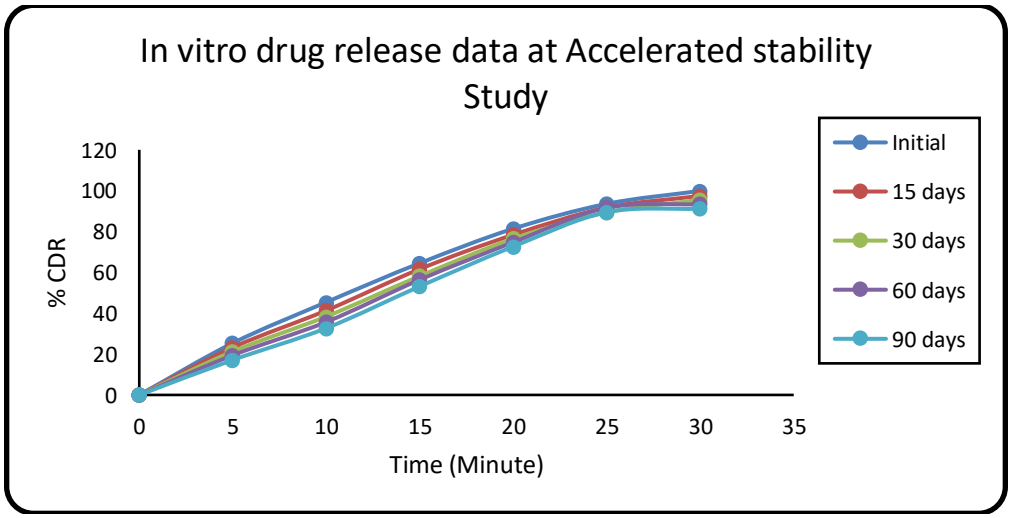

Fig. 11: *In vitro* release study of best formulation (TSF_{12}) at stressed condition

In vitro, drug release characteristics and physicochemical parameters did not significantly change for the optimal formulation (TSF_{12}) of ticagrelor sublingual tablets. After 90 days of exposure to an accelerated stress situation, more than 90% of the medication was still present in the body according to *in vitro* dissolution experiments. As a result, it was discovered that the sublingual pills under examination were stable for at least 3 months when stored under accelerated short-term settings. Table 5 presents the comparative physicochemical characteristics at various time intervals, and Figure 11 depicts the comparative release profile.

CONCLUSION:

Ticagrelor sublingual tablet formulations with various ratios of Crosscarmellose sodium, SSG, and cross povidone as super-disintegrants were designed, and formulated effectively. The drug and excipients are compatible with one another, and the formulation was thermally stable, according to FTIR and DSC investigations. Out of all the formulations created and tested, one stood out for having promising physicochemical properties, such as content homogeneity, tablet thickness, weight variation, friability, hardness, and disintegration. The TSF_{12} formulation was found to have the best *in-vitro* drug dissolution study when compared to other formulations because it released in bursts within the first five minutes and then completely within the following thirty. This may be because Crosscarmellose sodium and Cross povidone were combined as the super-disintegrant. The maximum amount of medicine was released within 30 minutes when the percentage of super-disintegrant was increased, however after it exceeded 4%, the tablet's hardness noticeably dropped and it became more friable. Combining the two super-disintegrants improves the medication release profile. Due to the existence of a lower percentage of super-disintegrants, the drug release rates of the TSF_1, TSF_4, and TSF_7 formulations were low. Because the regression value for the zero-order kinetic model was greater than that of the first-order kinetic model, it was determined from the in vitro release kinetic investigation that the release kinetic followed the zero-order kinetic model. Studies on stability were conducted under accelerated stability settings, and while all assessment parameters revealed a slight shift, they were still within acceptable bounds. According to the results of the aforementioned research, ticagrelor sublingual tablets are an appropriate formulation since they avoid the quick pass metabolism, increase the drug's bioavailability, and allow for a reduction in the overall daily dose.

ACKNOWLEDGMENT

The Hyderabad-based Dr. Reddy's Laboratories Pvt. Ltd., is grateful to the authors for giving free samples of medication and super-disintegrant so they could conduct their research. The chairman and principal of the Anwarul Uloom College of Pharmacy in Hyderabad, Telengana, are also acknowledged by the authors for granting permission to conduct the research.

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